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VIRAL DISEASES OF THE SKIN, 1975: A 25-YEAR PERSPECTIVE

HARVEY BLANK, M.D., AND HAROLD HAINES, PH.D.

Department of Dermatology, University of Miami School of Medicine, Miami, Florida, U. S. A.

Most of the major advances in modern virology during the past 25 years have been due principally to the development of refined laboratory techniques and tools and have provided a fund of new knowledge and information about the nature of viral infection and pathogenesis. One group of viruses of interest to dermatologists, the herpesviruses, is undergoing intensive biochemical investigation to determine whether it is carcinogenic. As a result of the success of the World Health Organization's campaign to eradicate smallpox, it is predicted that by the end of 1976, smallpox will have been eradicated.

Other viruses of dermatologic interest which are now being studied include the agents of warts, molluscum contagiosum, cat-scratch disease, and enteroviruses. Current research in the field of viral chemotherapy may provide the basis for successfully treating these diseases in the future.

Changing their role from hunters of microbes to biochemists probing into the nature of life, virologists are simultaneously reflecting and leading the revolution in biomedical research. By using the post-World War II tools of tissue culture, radioactive isotopes, chromatography, density gradient centrifugation, and the electron microscope, they have acquired a vast knowledge about the way viruses infect cells and cause disease. Unexpectedly the viruses themselves have emerged as powerful probes into the nature of cellular and life processes. Because of the necessarily close relationship between viruses and their host cells, the understanding and control of virus infections depend almost wholly on knowledge of cell biochemistry.

Vaccines and sera have been powerful aids in the prevention of such viral diseases as polio, measles, mumps, rubella, yellow fever, and hepatitis, but they are only extensions of the fundamental principles of Jenner's smallpox vaccine and Pasteur's rabies vaccine. Compared with the modern treatment of established diseases by means of specific chemotherapy, the management of viral diseases lags behind all other forms of chemotherapy even those of schizophrenia and cancer. Except for a few drugs, such as Marboran for smallpox, amantadine for influenza A_2, and possibly iododeoxyuridine for herpes simplex of the eye, no effective specific antiviral drug for systemic or topical use on human skin has been found.

Reprint requests to: Dr. H. Blank, Department of Dermatology, University of Miami School of Medicine, Miami, Florida 33152.

Abbreviations:
CMI: cell-mediated immunity
EB: Epstein–Barr virus
HSV: herpes simplex virus
PAC: papular acrodermatitis of childhood
VZ: varicella–zoster virus
ZIG: zoster immune globulin

A number of cutaneous viral diseases can be treated symptomatically or surgically, but even here, advances will be predictably slow until a great deal more is known about intricate cell mechanisms. The empiric, trial-and-error methods of screening compounds which produced sulfonamides, antibiotics, diuretics, and tranquilizers have failed to control virus infections. Perhaps useful drugs will be found only when cell biochemistry is well enough known to enable us to fashion precise "magic bullets" that will kill viruses without affecting the normal cell processes.

A detailed review of the many volumes and thousands of articles that have been written about the viruses which attack the skin is not feasible. Therefore, we have limited ourselves to a few details about each virus which we considered most important to dermatologists and future investigators. The few general references and very recent articles are meant to serve as guides to the original sources [1–4].

SMALLPOX

The universal dread of smallpox is well justified because, despite all modern supportive therapy, 10 to 25% of those who contract it die. The last epidemic occurred in 1972 in Yugoslavia where of the 175 people who contracted the disease 35 died. At the present time, the only small pockets of smallpox remaining are in India, Bangladesh, and possibly Ethiopia. Not a single case of smallpox has been reported in the United States for more than 25 years, but 5 to 10 people per year have died and many others have been made seriously ill by routine smallpox vaccination. Since 1971, however, routine vaccination in the United States and in many other countries has ceased. The eradication of smallpox is an exciting example of global cooperation in sharing the advances of medical science, epidemiology, and world politics.

Several years ago experts of the World Health Organization (WHO) concluded that smallpox could be eradicated by combining existing knowledge with a vigorous campaign in all countries where the disease existed. The scientific advances of that time seem rather simple now but were essential to the success of the campaign. First, when lyophylized vaccine supplanted glycerinized vaccine, a potent vaccine became available in the most remote areas of the world where no refrigeration exists. Second, it was deemed more practical and effective to contain outbreaks by vaccinating the inhabitants of areas where the disease existed than to vaccinate all of the inhabitants of a country or a continent. Third, it was discovered that smallpox is transmitted only by patients without any reservoir in insects or animals.

Because of the nature of the disease and the availability of effective prophylactic vaccines, WHO concluded that if total prevention could be achieved for one year, the disease would probably be abolished. The target date for this campaign was the end of 1975. Its incredible success in wiping out one of man's greatest scourges proves it to be one of the best investments and one of the greatest achievements in medical history.

MOLLUSCUM CONTAGIOSUM

The pathognomonic lesions of this disease are caused by one of the largest viruses that infect man [2]. Although the lesions contain millions of virus particles, the infectivity of the disease is surprisingly slight. Since most patients have no known contact with other patients with the disease, the mode of transmission often remains a mystery.

The incidence varies in different countries and with age, increasing noticeably at the time of onset of sexual activity. The distribution of cases by age follows a bimodal pattern. In children, molluscum lesions are scattered haphazardly over the trunk and extremities whereas in young adults the lesions occur in areas of genital contact and are found most commonly at the same age at which gonorrhea peaks. Some reports of transmission by wrestling and by experimental inoculation have appeared, but most often the source of infection is unknown.

Many sophisticated attempts to grow the molluscum virus have failed. The outer layers of the virus can be removed by tissue-cultured cells, but the DNA does not replicate and the virus does not reproduce in vitro.

Although the individual lesion is a small papule, it is probably not a true virus-induced tumor. Once removed, molluscum contagiosum lesions rarely recur. The best way to treat the disease is to paint each lesion very carefully with cantharidin (0.7%) in acetone and flexible collodion; sometimes the lesions must be covered with adhesive tape for 6 to 8 hr to get the desired response. Lesions which fail to respond or are missed can be re-treated at weekly intervals. Painful and multilating surgical procedures are rarely necessary.

ORF

Ecthyma contagiosum or orf is also caused by a large virus which has been studied with the electron microscope and in ovine tissue culture cells [2]. When contracted from animals, the human lesion resembles the chancriform group of anthrax, tularemia, and cat-scratch fever; only rarely does it cause a generalized vesicular dermatitis. There is no specific treatment.

HERPESVIRUSES

Because of their diversity, their complex interrelationship with their hosts, and the severe disease they cause, the group of viruses known collectively as the herpesviruses poses baffling but challenging problems which have prompted a crescendo of scientific and clinical research [4]. This interest has been heightened by the current theory which links herpesviruses with cancer in man and which has been corroborated by the fact that herpesviruses are known to cause cancer in other species. Great strides have been made in understanding the nature of herpesviruses, but no effective specific treatment has been found. Several new antiherpesvirus drugs are now being clinically tested.

Classification and Structure of Herpesviruses

Most of the animal species studied have one or more herpesviruses which are biologically and antigenically distinct from each other and from the herpesviruses of other animals. At least 39 herpesviruses are known to infect 22 species of warm- and cold-blooded animals [3]. Those which affect man are herpes simplex (HSV), varicella–zoster (VZ), cytomegalovirus, and the Epstein–Barr virus (EB), the cause of infectious mononucleosis and Burkitt's lymphoma. New strains are being discovered in other species.

The fact that herpesviruses, even those from diverse species, are morphologically similar makes electron microscopic diagnosis possible (Fig. 1). Though biologically and antigenically different from one another, they are all composed of an

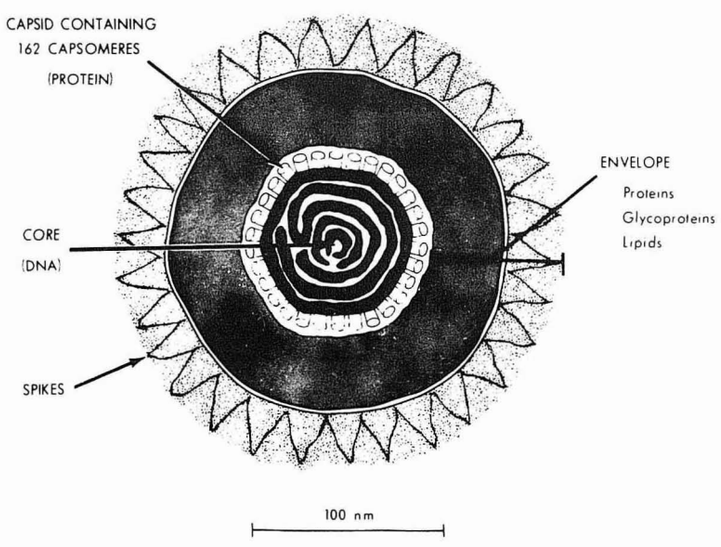

FIG. 1. Diagrammatic cross-section of the herpes simplex virus.

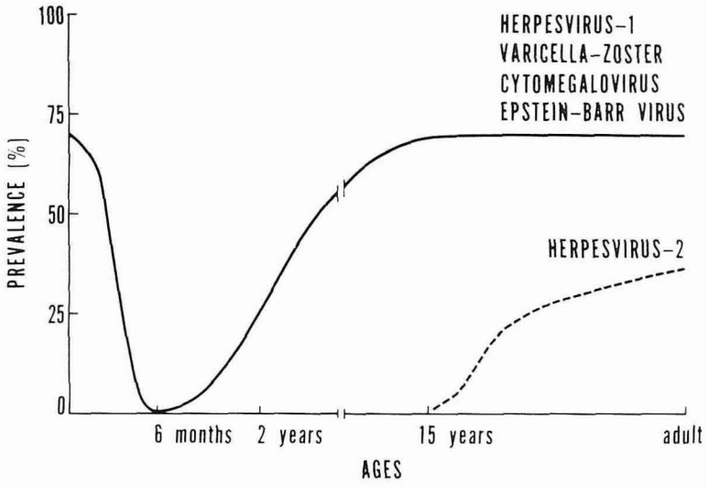

FIG. 2. Course of serum antibodies to herpes viruses.

icosahedral protein shell (capsid) around a nucleoprotein core which contains double-stranded DNA. The nucleocapsids themselves are enclosed in membranous structures which contain glycoproteins and proteins. The diameter of the enveloped particles is from 100 to 200 nanometers. Their complex structure is apparent from the at least 47 distinct polypeptides and glycoproteins in the envelopes of HSV [12].

Because the HSV and VZ viruses are of major interest in dermatology, we are limiting our discussion to them. The HSV and VZ infections in man have a few common characteristics. They occur as distinctive primary infections, often as acute gingivostomatitis with HSV or as chickenpox with VZ (Fig. 2). Later, after a variable latent period during which the virus remains quiescent in a regional ganglion, a recurrent form such as herpes labialis or zoster appears. Although high-titered neutralizing IgG antibodies appear with the infection, cell-mediated immunity (CMI) as well as interferon production may also play a role in healing the lesions. The details differ somewhat in the different clinical entities.

Herpes Simplex Virus

Detailed antigenic analysis has separted this virus into two distinct antigenic types, HSV-1 and HSV-2, which can also be distinguished by chemical differences in DNA. The two types first infect individuals at different times in life and are transmitted in different ways.

The clinical manifestations of herpes simplex (Fig. 3) are generally divided into (1) the primary infection, which occurs in a subject who has never been infected before and who therefore has no antibodies to the virus, and (2) the recurring infection, which occurs in those previously infected and with circulating antibodies to the infecting virus.

In the most common form of primary infection (HSV-1), which is subclinical and not apparent, the infected cells in the oral mucosa produce no clinical disease but circulating antibody titer to the virus increases. In approximately 10 to 15% of children, an acute gingivostomatitis occurs. Primary infection also appears as a respiratory infection, infected eczema, keratoconjunctivitis, or a fatal visceral disease of the newborn.

HSV-2 generally occurs on the genitalia after puberty, an indication that it is usually acquired by venereal contact. Rarely, an infant can contract HSV-2 from its mother's genital tract during birth. Although there is some crossover, HSV-1 and HSV-2 are immunologically separate. Thus, infection with type 1 virus does not protect from a mucocutaneous type 2 infection.

Until recently, recurrent lesions were thought to be caused only by reactivation of the latent virus (Fig. 4). However, experiments in which normal skin was inoculated with live herpesvirus demonstrated that infectious virus can reinfect a person who has high-titered neutralizing antibodies [5]. Thus, recurrent lesions from an exogenous source could occur when antibody is present. Since patients with recurrent herpes have maximum titers of neutralizing antibodies in their serum, injecting vaccines to increase serum antibodies would appear to be an irrational treatment.

Those who handle patients with herpes simplex should avoid reinfection of the fingers. Genital herpes or cervical lesions can probably occur from exogenous reinfections by sexual contact with an infected partner. Evidence from human and experimental studies indicates that after peripheral infection, the herpes virus lurks in some form in the regional nerve ganglia [6,7]. Many now believe that all recurrent herpes simplex originates in the ganglia and spreads distally to the skin. But this hypothesis does not answer all the questions. Although zoster may well follow this path, it is hard to understand how simplex lesions could appear on both sides of the face and still come from one ganglion. In addition to the bilateral nondermatome distribution, experimental reinfections in new sites (lip to arm or genitalia to thigh) not uncommonly result in spontaneous recurrent lesions in these inoculated sites. Do these recurrences come from infections lurking in newly

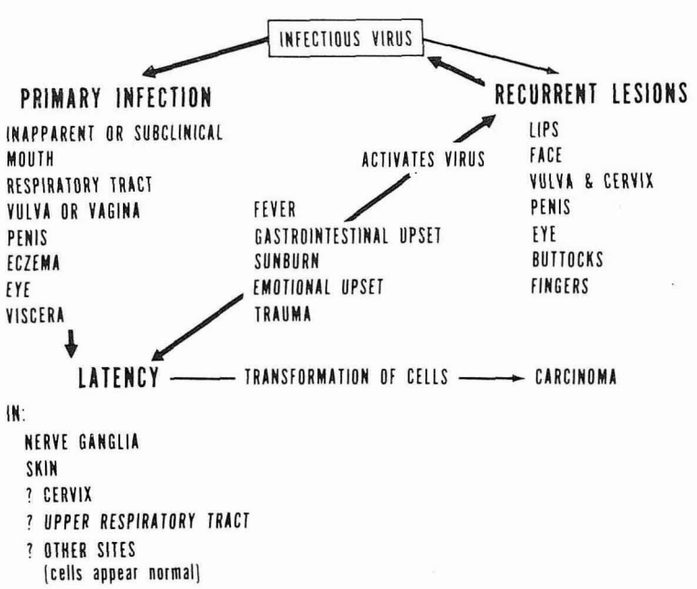

FIG. 3. Clinical events associated with herpes simplex infection.

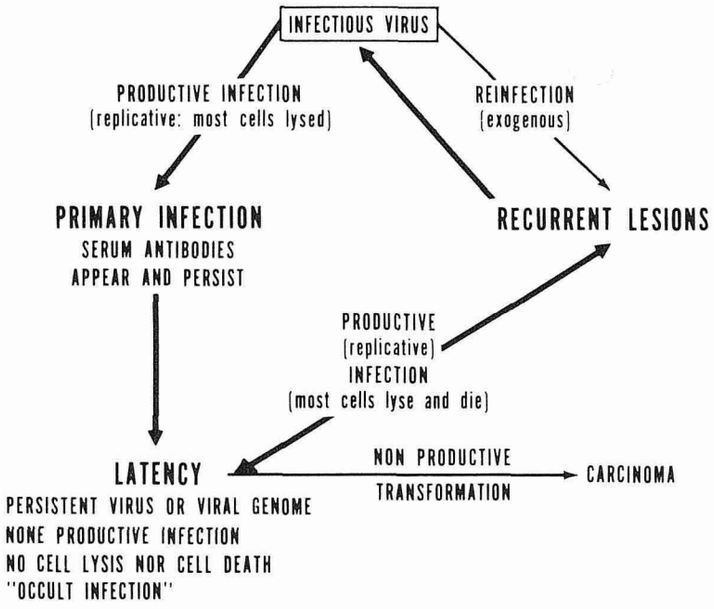

FIG. 4. Cellular events associated with herpes simplex infection.

infected ganglia and somehow are transmitted when high-titer neutralizing antibody is present? It would seem premature to abandon the skin as one of the potential sites of chronic viral genome between clinical attacks. Furthermore, if the virus were in the ganglia only between attacks, how could topical treatment to an active recurrent lesion prevent recurrences?

CMI may be important in recurring infections [8–11]. Although some of the data are contradictory, patients with recurrent lesions seem to have a lower level of CMI between attacks than normal seropositive controls. In patients receiving immunosuppressive agents after kidney transplants, HSV infections are often progressive [12], but they do not seem more common in patients with underlying lymphocyte defects [13]. Perhaps it would be worthwhile to study methods of increasing CMI in carefully controlled clinical trials.

Early reports of photochemotherapy of recurrent herpes simplex lesions were optimistic, but recent controlled studies have not only failed to show any benefit over the placebo but have indicated some disadvantages.

Herpesviruses and Cancer

Table I is a list of animal tumors caused by herpesviruses. EB virus is clearly associated with Burkitt's lymphoma, but the relation of HSV-2 to carcinoma of the cervix is still under investigation.

Several lines of evidence suggest that HSV-2 is causally related to cervical carcinoma [4]. According to epidemiologic studies, females with antibodies to HSV-2, which would indicate previous infection with the virus, have a higher incidence of cervical carcinoma than matched controls. In a study of cervical tumor, DNA isolated from the tumor contained about 39% of the herpesvirus DNA; this experiment, however, has not been confirmed. Other evidence comes from studies in which antigens produced by herpes simplex virus in cell culture are found to be related to antigens in cervical tumors or in the circulation of patients with tumors. An important piece of evidence is that inactivated herpes simplex virus can cause cancer in appropriate experimental animal models. Herpesviruses inactivated with ultraviolet light transformed cells in culture which later caused malignant tumors when injected into animals. The experiment can be repeated with both HSV-1 and HSV-2 and also with virus which has been inactivated with dyes and visible light. Because dye plus light makes herpesviruses carcinogenic in animals and because such treatment has not been proved effective in controlled clinical trials, most virologists are opposed to such therapy. In summary, although HSV-2 may be related to cervical cancer, it should be emphasized that only a small fraction of the women harboring HSV-2 develop cancer and that other factors are undoubtedly very important.

Treatment of Herpes Infections

The need for specific active treatment of herpes infections has steadily increased. Approximately 35% of all kidney transplant patients develop herpes simplex infections, many of which are life threatening [12]. Herpesvirus infections of atopic lesions may also pose a threat to life. Patients who have frequent recurrent herpes simplex of the face or of the genitalia, as well as women with cervical erosions or other forms of cervical abnormalities that may be due to herpesvirus infection, urgently need treatment.

A large number of drugs have been tested and have proved ineffective, if not downright harmful, in herpes simplex. As with other virus infections, once the disease is clincally apparent, chemotherapy and even specific antisera are of no benefit. (See Table II for symptomatic treatment.)

Varicella-Zoster Virus

Two different clinical diseases are caused by the VZ virus and appear to result from the immune status of the patient at the time the virus manifests itself. The primary infection, varicella, probably occurs via the upper respiratory tract and, in the absence of antibody, spreads hematogenously to the skin, mucosa, and deeper tissues. Zoster, on the other hand, is presumably caused by the recrudescence of the same VZ virus infection later in life. The viral agent probably resides in a latent form, which has not been found but which proba-

TABLE I. *Herpesviruses and neoplastic disease*

Species	Tumors
Chicken	Marek's disease (lymphoma)
Frog	Lucke's adenocarcinoma
Monkey	Lymphoreticular tumors
Rabbit	Malignant lymphoma
Human	Burkitt's lymphoma
Human	Carcinoma cervix

TABLE II. *Treatment for cutaneous herpes simplex*

Specific
None proved effective in controlled trials
Eliminate inciting ("trigger") factor if possible
Symptomatic
Early stages—tingling, papules, vesicles
Apply alcohol, ether, chloroform, or liquid nitrogen
Open all vesicles and expose to warm lamp
Later stages—crusting, itching
Apply emollient ointment or cream
For mouth lesions
Viscous lidocaine solution as a rinse
Severe primary or disseminated cutaneous infection
Parenteral fluids
Systemic analgesics
Agents which may warrant further topical controlled trials
AraA (adenine arabinoside: 9-β-D-arabinofuranosyl adenine)
Phosphonoacetic acid
2-Deoxy-D-glucose
Poly I:C

bly lies in the dorsal root ganglion cells or skin cells and travels from one site to the other.

VZ virus is highly infectious in human vesicle fluid and very easily infects susceptible cells in culture. However, such infected cells do not yield virus particles with high infectivity, and, therefore, VZ virus is difficult to work with in the laboratory. Unlike the two distinct antigenic strains of herpes simplex virus, the two strains of VZ virus, varicella or zoster, cannot be distinguished by antigenic means; in fact, very little is known about the antigenic makeup of the virus.

Usually most patients who develop zoster are apparently healthy, and no trigger factors can be found. However, patients with underlying malignant diseases who are treated with antimetabolites, x-rays, and alkylating agents form a high-risk group. They are susceptible to a form of disseminated VZ infection which is sometimes fatal. Patients with defects in CMI such as Hodgkin's disease, malignant lymphoma, and chronic lymphatic leukemia are more susceptible to zoster, but those with humoral defects such as multiple myeloma are not [14].

Little is known about the role played by CMI or interferon in VZ virus infection. Some patients with underlying serious illnesses who developed zoster had low levels of cutaneous interferon which were often associated with viral spread and death. Those who were not leukopenic and developed interferon in the vesicle fluid recovered. High levels of interferon are found in the vesicle fluid of normal subjects with varicella.

Despite experiments with drugs that affect DNA synthesis, specific treatment for VZ infection is still lacking. Analgesics or a tranquilizer like chlorprothixine give symptomatic relief; trials with interferon inducers remain inconclusive. Zoster immune globulin (ZIG), which prevents varicella in children with an underlying ailment who have been exposed to chickenpox, is available from the Communicable Disease Center in Atlanta. Once clinical disease has appeared, however, it is of no benefit for zoster or varicella.

To reduce the risk of postzoster neuritis, systemic corticosteroids should be given to patients over 60 years of age unless there is a strong contraindication. Prednisone (120 mg per day for a week, 60 mg per day for each of the next 2 weeks) is usually recommended [2].

WARTS

Although the human wart virus could not be grown outside its natural human host until 1975, its natural history and biology are well known. Some observations, such as the high incidence of warts in slaughter-house workers, remain enigmatic. In the majority of patients, the lesions disappear spontaneously within a year or two of initial infection. The success of various forms of treatment probably depends to a great extent on natural involution. Even after deep destructive methods of treatment, approximately one-third of the lesions will reappear; therefore, no treatment that would produce permanent scars should be used.

The infectious transmission of warts has been documented for more than half a century, but not until recently was it clear that skin warts and genital warts are probably caused by closely related but different viruses. The recent increase in genital warts (1.5% of obstetrical patients have them) has paralleled the increase in gonorrhea and other veneral infections. Genital warts in the female become large apparently from increasing levels of estrogen. Large vulvar warts usually indicate pregnancy or serious liver disease; if they become exceptionally large in pregnant women, they may be a hazard at delivery because of the danger of hemorrhage. Another hazard is to infants born of mothers with condyloma acuminatum. Such children may develop laryngeal papillomas which are apparently caused by the wart virus. If these spread, they cause airway obstruction and death by suffocation [15]. Another hazard to pregnant women that has been reported is the copious treatment of moist warts with podophyllin. Absorption and life-threatening toxicity of the central nervous system of the mother and the death of the fetus have occurred. Veneral disease centers have observed that anal warts and genital warts are about equally frequent in both men and women, but when perianal warts occur alone without genital warts, the vast majority are found in male homosexuals, an observation known to the second-century Romans.

The treatment of warts has not advanced significantly since Mark Twain's day except for the simplified advance of liquid nitrogen over burning

needles. The use of liquid nitrogen can, however, result in the transmission of warts to other sites or to other patients from contaminated applicators. Although no specific chemotherapy has yet been devised, recent studies indicate that topically applied 5% fluorouracil, usually with occlusion, (danger: onycholysis) is more effective than placebos. However, one-third of the lesions fail to clear, and onycholysis is always a danger when periungual warts are treated. Topical bleomycin and 20% iododeoxyuridine may also prove to be effective caustics.

When the human papilloma virus was first demonstrated with the electron microscope, it was exciting confirmation that this truly is an infectious disease. Despite many attempts, the virus could not be grown in tissue culture or in other animals. Purification of the virus by Pass and his associates [15] and others has provided very high concentrates of virus for immunologic studies and cultivation. The immunologic studies with purified wart virus antigen have been somewhat contradictory [13,15,16]. Some investigators report that circulating antibodies to the wart virus increase as the warts disappear, but others suggest that antibodies appear as the infection continues. Many patients with warts, even extensive warts, fail to develop any detectable antibody by present methods, and there is little evidence of any relationship between circulating antibody and protection against warts, their duration, or their spontaneous involution. The fact that injecting purified human virus subcutaneously into guinea pigs regularly results in antibody formation whereas it fails to do so in normal epithelial infections suggests that antigen often fails to penetrate the epidermis in normal infections. There is some evidence that a defective immune state such as Hodgkin's disease, malignant lymphoma, or chronic lymphatic leukemia may predispose to warts [13], which are also more likely to develop in patients with renal transplants. Although these groups are more susceptible, it is not known whether CMI is important in natural involution. According to another intriguing study with enzyme markers, each wart arises from a single clone of cells. This important finding should be verified since it could also explain the spontaneous dissappearance of one of several warts by the senescence of one clone but not others in the absence of an immune mechanism.

Eisinger and her co-workers [17] have reported on the propagation of human wart virus in tissue culture. They provide firm evidence that human wart virus multiplied in tissue culture for at least 14 passages. The techniques of the tissue culture seem to be unique; it is to be hoped that the results can be promptly confirmed. Lancaster and Menke from the Scripps Clinic have reported on the persistence of viral DNA in human cell cultures infected with human papilloma virus [14]. Although these cells seem to have normal growth and morphology, under proper conditions the latent viral DNA might become derepressed and induce cell growth similar to that of transformed cells. These results would indicate that the ubiquitous human wart virus should be seriously considered as the agent of other neoplastic diseases in man. At any rate, it now seems possible that the viral DNA can be transmitted in culture and that an apparently intact infectious virus will be available for experimental studies.

PAPULAR ACRODERMATITIS OF CHILDHOOD (AN AUSTRALIA ANTIGEN DISEASE)

In 1955 Gianotti of Milan described papular acrodermatitis of childhood (PAC) and since then it has been reported from many other countries [18]. It is an infective disease with a recognizable papular eruption lasting 20 days or more, reactive reticulohistiocytic lymphadenitis that is mainly inguinal and axillary, and an acute hepatitis, usually anicteric, which commonly lasts about 2 months. In all cases, Australia antigen is present in the blood; it can be detected 10 or more days after the onset of the disease and persists from months to years afterwards. The children are not usually very sick but older ones may develop some icterus. The eruption consists of monophoric lenticular, flat, erythematopapular, nonitching lesions, symmetrically spread over the face, buttocks, and limbs. The trunk is usually spared but a transient rash may be seen on it in the early eruptive phase. The mucous membranes are not affected.

CAT-SCRATCH DISEASE

Cat-scratch disease, which is somewhat rare, has distinctive and intriguing features. Lee Foshay in the United States and Robert Debré in Paris studied several cases with characteristic peripheral lesions and regional lymph nodes from which they prepared a skin test antigen. When the two workers exchanged antigens, they found that the American antigen was positive in French patients and the French antigen active in American patients. Cat-scratch disease appears to have a single common cause, but the many attempts to isolate a virus and to find other causative organisms have been unsuccessful.

Diagnosis is based on the typical clinical course because the skin test antigen is not generally available. The lesion is a small pink macule to papule, usually on the hand, which appears about 3 to 14 days after inoculation. Usually 3 weeks after the primary lesion, adenitis appears, most often in the axilla; however, if the primary lesion is missed, the adenitis may constitute the whole disease. It is never bilateral and is characterized as indolent, nearly painless, and varying in size from a cherry to an orange. Within a few weeks, it slowly reabsorbs but in about half the patients it suppurates and even drains if the pus is not aspirated. As a rule, fever and general symptoms occur for brief periods. Involvement of the visceral and central nervous systems occurs but only rarely. No effective treatment has been found, but specific sero-

logic tests, as well as a skin test, are available in research laboratories which use antigen prepared from lymph node pus. Although cats seem to transmit the disease, they are not the causative agent but play the role of a vector and inoculator. In some authentic cases, the patients had had no contact with a cat.

LUPUS ERYTHEMATOSUS

Although many of the lesions of lupus erythematosus can be accounted for by a process participated in by antigen–antibody complexes, several studies suggest that certain viruses also play a role in its initiation or pathogenesis. In addition to the electron microscopic findings of virus-like tubules which, however, were never proved to be viruses, several studies in NZB mice and in dogs have implicated viruses. The authors have stressed that viral infection cannot be the sole cause of lupus erythematosus, especially since the studies of NZB mice have demonstrated the importance of a genetic factor that could be expressed by an unbalanced immune system. The lupus-like disease of dogs is still being studied and it has been reviewed by Schwartz [19]. Zhdanov has reported that DNA sequences homologous to the RNA of

TABLE III. *Mucocutaneous patterns in Coxsackie and Echo virus infections*[a]

Disease	Skin lesions	Mucosal lesions	Virus group and type
		Coxsackie Viruses	
Herpangina	Usually none	Few (4–10) vesicles progressing to ulcers (3–6 mm) with hyperemic border; of mouth and soft palate, uvula, anterior pillars, pharynx	A 9, 2, 4, 5
Hand, foot and mouth disease	Few (2–5) papulovesicles lateral proximal border of fingers and ulnar borders of hands; many tiny vesicles may occasionally be seen on palms, feet; similar vesicles on toes and lateral borders. Maculopapular and vesicular lesions common on buttock under age 3.	Herpangina-like; all areas except posterior pharynx	A 16, 5
	Maculopapules; petechiae occasionally; urticarial lesions; rarely vesicles resembling varicella. First face, trunk, and then generalized.	May be herpangina-like	A 9
	First face, trunk, and then generalized. Maculopapules (morbilliform).	Usually none	A 4
	Morbilliform macular and papular which appears as fever subsides (like roseola). First face, trunk, then generalized.	Vesicular, pharyngitis with type 5	B 1, 3, 4, 5
		Echo Viruses	
Echo 9	Maculopapular, sometimes vesicular. If petechial, look for meningococcemia. Face, neck, then generalized.	Occasionally punched-out ulcers on soft palate and tonsillar pillars; grayish or white dots simulating Koplik's spots	9, 4, 6, 14, 18 (and others cause erythema and/or vesicles)
Boston exanthem	Maculopapular rash appears as febrile response diminishes. First face, neck, then generalized.	Punched-out ulcers on soft palate and tonsillar pillars	16, 1, 2, 3, 5, 7, 11, 19

[a] Derived in part from: Debré R, Celers J: Clinical Virology, Philadelphia, Saunders, 1970, pp 374–384.

measles virus were found in tissues affected with systemic lupus erythematosus. Integrated viral genomes of such paramyxoviruses as measles could be expressed by synthesizing cell membranes with altered antigenic properties which would then become targets for the host's immunocompetent T-cells and would trigger autoimmune disease [20].

ENTEROVIRUSES

In Table III, the multitude of mucocutaneous lesions associated with Coxsackie and Echo viruses are tabulated.

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